

REMARKS

Reconsideration of the subject matter identified in caption, pursuant to and consistent with 37 C.F.R. §1.112 in light of the remarks which follow is respectfully requested.

As correctly indicated in the Office Action Summary, claims 42-55 are pending in the instant application. By the present Amendment, claims 56-59 are added. Claims 56-59 are directed to methods of treatment of different conditions using specific species of compounds as disclosed in the specification and in the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez. The new claims have basis at least in claims 42-55 and on pages 26-40 of the specification as originally filed. The species are named at on least on pages 11 and 12 of the specification and in the Examples. No new matter has been introduced.

INFORMATION DISCLOSURE STATEMENT

The outstanding Office Action indicates that the references submitted in the Information Disclosure Statement (IDS) filed on February 5, 2001 have been stricken, because the IDS purportedly does not clearly indicate that only abstracts were submitted. Applicants respectfully submit a new IDS, attached hereto, which cites the references of the previous IDS in the format suggested by the Examiner. This new IDS also includes two new references, which are cited in this Reply and Amendment.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 42-55 stand rejected under 35 U.S.C. §112, first paragraph, as purportedly containing subject matter which was not adequately described in the specification.

Specifically, it is purportedly unclear whether the compounds of the claimed invention are retinoids and/or share properties with retinoids, as well as whether it is the presence or absence of these properties which correlate with the effectiveness of compounds in therapeutic applications. This rejection is respectfully traversed.

The outstanding Office Action states that although Applicants have asserted that the claimed compounds are retinoids, there is no agreed upon "standard as to what the structural, biochemical or physical properties might be that are either necessary or sufficient for a compound to be classified in this way". See Office Action, pages 5-6. Applicants submit that the term "retinoids" has the same meaning for all scientists and researchers, regardless of what area of science they study, and that this meaning is well known to those in the art. "Retinoids" are defined as naturally occurring and synthetic compounds with vitamin A activity. *Fitzpatrick's Dermatology in General Medicine* (5th Ed., Vol. II, Ch. 245, page 2726) defines retinoids as "both the naturally occurring compounds with vitamin A activity and to synthetic analogs of retinol." *The Retinoids, Biology, Chemistry and Medicine* (2d Ed., Ch. 8, page 319) defines retinoids as "vitamin A and its natural and synthetic derivatives".

Further, retinoid action can be characterized by study of nuclear retinoid receptors known as retinoid acid receptors (RARs) or retinoid X receptors (RXRs). In the presence of retinoid, the RARs and the RXRs bind specific DNA regulatory sequences and thereby

activate specific sets of genes. RARs bind to regulatory regions of DNA called retinoic acid response elements (RAREs) or target sequences, and activate gene transcription in a ligand dependent manner. The receptor domain that binds to DNA is distinct from that which binds the ligand. RARs bind to their response elements as dimers. RXRs are the key partner for heterodimerization and ultimate functioning of RARs. *See Fitzpatrick's Dermatology*, (Ch. 256, page 2810).

A retinoid can have selectivity for RARs (like all trans-retinoic acid) or for RXRs, but some retinoids can activate both RXRs and RARs (such as 9-cis retinoic acid) and have no selectivity. *See* Examples 2 and 4 of the present invention. Agonist RARs activate RARs, agonist RXRs activate RXRs and panagonist RARS/RXRs activate both receptors.

Further, the actions and effects characteristic of all retinoids, as well as various diseases which respond to retinoids, are also known in the art. Retinoids and retinoic compounds, such as RARs and RXRs, are effective in the differentiation and proliferation of cells, and so can be useful to treat a multitude of diseases. *Fitzpatrick's Dermatology* (page 2810) discloses that "retinoids have diverse biologic effects. They affect cell growth and differentiation, morphogenesis, inhibition of tumor production and malignant cell growth, immunomodulatory actions and alterations in cellular cohesiveness". Table 256-1 describes the list of retinoid-responsiveness dermatological diseases. *See* page 2811. In *The Retinoids* (Ch. 8, page 319), "Vitamin A and its natural and synthetic derivatives (retinoids) are required for several essential life process, including vision, reproduction, metabolism, differentiation, hematopoiesis, bone development and pattern formation during embryogenesis. There is also considerable evidence that retinoids have potent

antiproliferative effects, and may be effective in the treatment of a variety of human diseases including cancer.” Chapter 11 discloses a list of effects of retinoids on the activity of several factors, hormones, enzymes and cells that interact in many metabolic processes and diseases. Pages 444-445 disclose the activity of retinoids in carcinogenesis, and the actions of retinoids as mediators of cellular proliferation and differentiation. *The Retinoids* (pages 597-598) further disclose that “the capacity of retinoids to modulate the differentiation and proliferation of both preneoplastic and neoplastic cells is an important biologic property of these substances”, and that retinoids are useful in treating and preventing cancer. Lippman, Giovanni, Kavanagh and Meyskens do not directly disclose synthetic retinoid RARs or RXRs but the natural retinoid like all-trans or 9-cis retinoic acid, but disclose that retinoids can be used for treating some diseases.

Applicants would like to further clarify the utility of the F9 PA induction assay with regard to retinoic compounds, as utilized in the data disclosed in the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez. This test does not refer to treatment of disorders, but instead to the identification of RARS-type antagonists. In Bailly *et al.*, when the author says “the mechanism of PA induction by retinoids has not been elucidated”, it does not mean that the compounds are inactive on the PA, but rather that the mechanism of action is not known. “The capacity of each retinoid to induce a biological response...affinity” means that this test doesn’t demonstrate a biological activity, but just that the potency (AC_{50}) or the affinity (IC_{50}) of the retinoid for endogenous RA receptors.

Levin and Allenby disclose that RXRS compounds can be identified by this method, as well as the specific binding and transactivation assays. The RXRS binding tests the

capacity of the compound to bind to RXRs and the results are calculated in K_d or IC_{50} which represents the concentration required to produce a 50% inhibition of binding. The RXRS transactivation demonstrates the activity of the compound by a cotransfection assay. The results may be explained by a percentage of activation or by an AC_{50} , which is the 50% activation concentration.

Thus, Applicants respectfully submit that the conclusion that the compounds disclosed in the present invention are retinoids is reasonable and supported by the knowledge of retinoids of those skilled in the art. Further, Applicants submit that as all retinoids are known by those in the art to share certain characteristics and actions, it is reasonable to conclude that the retinoids of the present invention also share these properties, including the therapeutic actions.

However, Applicants respectfully note that the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez also supports the above arguments, and sets forth data showing that the compounds of the present invention are retinoids and that retinoids are known to share therapeutic properties. As this document was a signed Declaration by an expert, the contents of the declaration should have been taken truth and given weight.

A declaration filed under 37 C.F.R. § 1.132 is, itself, evidence which must be considered. The weight given to a Declaration depends on the evidence presented therein. *See In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Applicants submit that the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez was not merely an assertion of facts, but rather presented scientific reasoning as well as data supporting the conclusions of Dr. Demarchez. In particular, the Declaration

supports the conclusion that several compounds of the claimed invention have been demonstrated to have biological activity as RARS type agonists, RXRS agonists or both. The Declaration also provides a discussion of published references that document the well known scientific finding that retinoids have established utility as therapeutic agents. Further, the Declaration provides the results of *in vivo* assay tests showing how a compound of the claimed invention has biological activity in ear oedema. Accordingly, the Declaration of Dr. Demarchez should have been given weight by the Examiner.

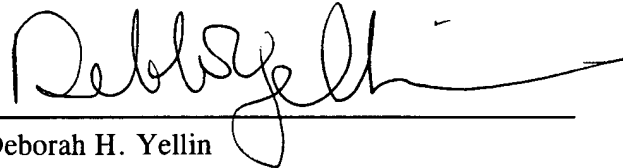
Thus, based on the above remarks, Applicants respectfully submit that the efficacy of retinoid compounds as pharmaceutical agents is accepted in the art. Applicants further submit that it is reasonable to conclude that they will exhibit desirable pharmacological properties and be useful in the treatment of the recited conditions, and that the compounds of the claimed invention may be used in treatment of the claimed conditions. Accordingly, withdrawal of the rejection of claims 42-55 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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